1 Name of the Medicine

Roxysaf 150mg Tablets

2. Qualitative and Quantitative Composition

Each Film Coated tablet contains Roxithromycin 150mg as an active ingredient.

3. Pharmaceutical form:

White, round, biconvex coated tablet and engraved SFN on one side.

4. Clinical particulars

4.1 Therapeutic indications

Adults

Roxysaf is indicated for the treatment of the following types of mild to moderately severe infections in adults caused by or likely to be caused by susceptible micro-organisms:

- Upper Respiratory Tract Infections: acute pharyngitis, tonsillitis, sinusitis
- Lower Respiratory Tract Infections: acute bronchitis and acute exacerbations of chronic bronchitis; community acquired pneumonia
- Skin and skin structure infections
- Non gonococcal urethritis

Children

Roxysaf 150mg tablets are indicated for the treatment of the following mild to moderately severe infections in children caused by or likely to be caused by susceptible micro-organisms:

- Acute pharyngitis
- Acute tonsillitis
- Impetigo

Appropriate culture and sensitivity tests should be performed when necessary to determine an organism's susceptibility and thus treatment suitability. Therapy with roxithromycin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

4.2 Posology and Method of Administration:

Adults

Roxysaf should be taken at least 15 minutes before food or on an empty stomach (*i.e.* more than 3 hours after a meal).

The Recommended dose is 150mg BD.

Roxysaf 150mg Tablets	
Usual dosage	One tablet twice daily or Two tablets once daily
Elderly	One tablet twice daily or Two tablets once daily
Impaired renal function	One tablet twice daily or Two tablets once daily

BODYWEIGHT	**Roxysaf 150mg Tablets**
6 - 11 kg	Half a tablet morning and evening
12 - 23 kg	One tablet morning and evening
24 - 40 kg	Two tablets morning and evening
> 40 kg	One tablet morning and evening

4.3 CONTRAINDICATIONS

• Known hypersensitivity to macrolides, including erythromycin.
• Severely impaired hepatic function.
• Concomitant therapy with vasoconstrictive ergot alkaloids

4.4 Special Warnings and Precaution for Use:

The safety of roxithromycin has not been demonstrated in patients with impaired hepatic or renal function. Caution should be exercised if roxithromycin is administered to patients with impaired hepatic or renal function. If administered to patients with severe impaired hepatic function (e.g. hepatic cirrhosis with jaundice and/or ascites), the dose should be reduced by half.
Renal excretion of roxithromycin and its metabolites accounts for a small percentage of an oral dose. The dosage should be kept unchanged in renal insufficiency. Prolonged or repeated use of antibiotics including roxithromycin may result in superinfection by resistant organisms. In the event of superinfection, roxithromycin should be discontinued and appropriate therapy instituted.

When indicated, incision, drainage or other appropriate surgical procedures should be performed in conjunction with antibiotic therapy.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the

colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases, appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement therapy should be provided when indicated.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (LOMOTIL®), may prolong and/or worsen the condition and should not be used.

Roxithromycin, like erythromycin, has been shown *in vitro* to elicit a concentration - dependent lengthening in cardiac action potential duration. Such an effect is manifested only at supra – therapeutic concentrations. Accordingly, the recommended doses should not be exceeded.

In certain conditions macrolides, including roxithromycin, have the potential to prolong the QT interval. Therefore roxithromycin should be used with caution in patients with congenital prolongation of the QT interval, with ongoing proarrhythmic conditions (i.e uncorrected hypokalemia or hypomagnesaemia, clinically significant bradycardia), and in patients receiving Class IA and III antiarrhythmic agents and drugs such as astemizole, cisapride or pimozide.

Use in Children

In young animal studies, high oral doses of roxithromycin were associated with bone growth plate abnormalities. However no abnormalities were observed in the animals at doses resulting in unbound plasma roxithromycin concentrations that were 10 to 15 times higher than the unbound concentration measured in children receiving the therapeutic dose.

The maintenance of such safety margins is primarily dependent on high affinity binding of roxithromycin to plasma alpha-1-acid glycoprotein and will be compromised by any circumstances attenuating the extent of this binding. It is recommended that the approved paediatric dosage regimen (i.e. 5 to 8 mg/kg/day for a maximum of 10 days) be adhered to strictly.

Neutropenia was observed in children treated with roxithromycin. 31.6% of 402 children in clinical trials had a neutrophil count below the lower limit of the normal range (3500/mm3) at the conclusion of therapy with roxithromycin. Of these, 4% had a neutrophil count of less than 1500/mm3 and 1.2% had a count of less than 1000/mm3. It is not known whether this is an effect of the drug or whether it reflects a normal fluctuation of the neutrophil count or a response to infection in children.

Use in Pregnancy (Category B1)

Reproductive studies in rats, mice and rabbits at doses of 100, 400 and 135mg/kg/day, respectively, did not demonstrate evidence of developmental abnormalities. In rats, at doses

above 180mg/kg/day, there was evidence of embryotoxicity and maternotoxicity. The safety of roxithromycin for the human foetus has not been established.

Use in Lactation

Small amounts of roxithromycin are excreted in the breast milk. Breast feeding or treatment of the mother should be discontinued as necessary.

Use in the Elderly

No dosage adjustment is required in elderly patients.

4.5 Interactions with Other Medicines

Roxithromycin has a much lower affinity for cytochrome P450 than erythromycin and consequently has fewer interactions. Interactions may be observed, however, with drugs that bind to alpha-1-acid glycoprotein, such as disopyramide.

Roxithromycin does not appear to interact with oral contraceptives containing oestrogens and progestogens, prednisolone, carbamazepine, ranitidine or antacids.

Theophylline

A study in normal subjects concurrently administered roxithromycin and theophylline has shown some increase in plasma concentration of the latter. While a change in dosage is usually not required, patients with high levels of theophylline at commencement of treatment should have levels monitored.

Ergot Alkaloids

Reactions of ergotism with possible peripheral necrosis have been reported after concomitant therapy of macrolides with vasoconstrictive ergot alkaloids, particularly ergotamine and dihydroergotamine. Because a clinical interaction with roxithromycin cannot be excluded, administration of roxithromycin to patients taking ergot alkaloids is contraindicated. Absence of treatment with these alkaloids must always be checked before prescribing roxithromycin.

Disopyramide

An *in-vitro* study has shown that roxithromycin can displace protein bound disopyramide; such an effect *in vivo* could result in increased serum levels of disopyramide. Consequently ECG and, if possible, disopyramide serum levels should be monitored.

Terfenadine

Some macrolide antibiotics (*eg.* erythromycin) may increase serum levels of terfenadine. This can result in severe cardiovascular adverse events, including QT prolongation, *Torsades de Pointes* and other ventricular arrhythmias. Such a reaction has not been documented with roxithromycin which has a much lower affinity for cytochrome P450 than erythromycin. However, in the absence of a systematic interaction study, concomitant administration of roxithromycin and terfenadine is not recommended.

Astemizole, Cisapride, Pimozide

Other drugs, such as astemizole, cisapride or pimozide, which are metabolized by the hepatic isozyme CYP3A4, have been associated with QT interval prolongation and/or cardiac arrhythmias (typically *Torsades de Pointes*) as a result of an increase in their serum level subsequent to interaction with significant inhibitors of this isozyme, including some macrolide antibacterials. Although roxithromycin has no or limited ability to complex CYP3A4 and therefore to inhibit the metabolism of other drugs processed by this isozyme, a potential for clinical interaction of roxithromycin with the above mentioned drugs cannot be either ascertained or ruled out in confidence; therefore, concomitant administration of roxithromycin and such drugs is not recommended.

Roxithromycin, like other macrolides, should be used with caution in patients receiving class IA and III antiarrhythmic agents.

Vitamin K Antagonists

While no interaction was observed in volunteer studies, roxithromycin appears to interact with warfarin. Increases in prothrombin time (international normalized ratio; INR) have been reported in patients treated concomitantly with roxithromycin and warfarin or the related Vitamin K antagonist phenprocoumon, and severe bleeding episodes have occurred as a consequence. INR should be monitored during combined treatment with roxithromycin and Vitamin K antagonists.

Digoxin and Other Cardiac Glycosides

A study in healthy volunteers has shown that roxithromycin may increase the absorption of digoxin. This effect, common to other macrolides, may very rarely result in cardiac glycoside toxicity. This may be manifested by symptoms such as nausea, vomiting, diarrhoea, headache or dizziness; cardiac glycoside toxicity may also elicit heart conduction and/or rhythm disorders. Consequently, in patients treated with roxithromycin and digoxin or another cardiac glycoside, ECG and, if possible, the serum level of the cardiac glycoside should be monitored; this is mandatory if symptoms which may suggest cardiac glycoside overdosage occur.

Midazolam

Roxithromycin, like other macrolides, may increase the area under the midazolam concentration-time curve and the midazolam half-life; therefore the effects of midazolam may be enhanced and prolonged in patients treated with roxithromycin. There is no conclusive evidence for an interaction between roxithromycin and triazolam.

Theophylline and Ciclosporin

A slight increase in plasma concentrations of theophylline or ciclosporin A has been observed. This does not generally necessitate altering the usual dosage.

CYP3A

Roxithromycin is a weak CYP3A inhibitor. The effect of roxithromycin on exposure to drugs predominantly cleared by CYP3A metabolism would be expected to be 2-fold or less. Caution should be exercised when roxithromycin is concomitantly prescribed with drugs metabolized by CYP3A (such as rifabutin and bromocriptine).

4.6. Carcinogenesis, Mutagenesis and Effects on Fertility

Long term studies in animals have not been performed to evaluate the carcinogenic potential of roxithromycin. Roxithromycin has shown no mutagenic potential in standard laboratory tests for gene mutation and chromosomal damage.

There was no effect on the fertility of rats treated with roxithromycin at oral doses up to 180mg/kg/day.

4.7. Effects on Ability to Drive and use Machinery

Attention should be drawn to the possibility of dizziness, visual impairment and blurred vision.

4.8. Adverse Effects

Roxithromycin is generally well tolerated. In clinical trials, treatment discontinuation due to adverse effects occurred in only 1.2% of adult patients and 1.0% of children. The following side-effects or serious adverse events possibly associated with roxithromycin have been reported:

Gastrointestinal

Nausea, vomiting, epigastric pain (dyspepsia), diarrhea (sometimes containing blood), anorexia, flatulence, pseudomembranous colitis. In clinical studies, the incidence of gastrointestinal events was higher with the 300 mg once daily dosage regimen than with 150 mg twice daily. Symptoms of pancreatitis have been observed; most patients had received other drugs for which pancreatitis is a known adverse effect.

Hypersensitivity

Urticaria, rash, pruritus, angioedema. Rarely, serious allergic reactions may occur such as asthma, bronchospasm, anaphylactic-like reactions, anaphylactic shock, purpura, glottic oedema, generalised oedema, erythema multiforme, exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome and Toxic Epidermal Necrosis (TEN).

Liver

Moderate increase in serum transaminases, AST-ALT and/or alkaline phosphatase levels have been observed and are somewhat more likely to occur in the elderly (> 65 years of age). Acute cholestatic hepatitis and acute hepatocellular injury (sometimes with jaundice), are rarely reported.

Others

Eosinophilia, agranulocytosis, neutropenia, thrombocytopenia, bronchospasm, hallucination, confusion, headache, dizziness, paraesthesia, tinnitus, malaise, moniliasis, pancreatitis, QT prolongation, disorders of taste and/or smell, visual impairment, blurred vision, temporary deafness, hypoacusis and vertigo.

Prolonged use of antibiotics including roxithromycin may result in superinfection; overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. In the event of superinfection, appropriate measures should be taken.

4.9 Overdose:

In case of over dosage: gastric lavage and symptomatic treatment: there is no specific antidote.

Poison Schedule of the Medicine

S4 (Prescription Only Medicine)

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Macrolides antibiotics

ATC Code: J01FA06

Mechanism of Action:

Roxithromycin prevents bacteria from growing, by interfering with their protein synthesis. Roxithromycin binds to the subunit 50S of the bacterial ribosome, and thus inhibits the synthesis of peptides. Roxithromycin has similar antimicrobial spectrum as erythromycin, but is more effective against certain gram-negative bacteria, particularly *Legionella pneumophila*.

Spectrum of Antimicrobial Activity

The critical concentrations differentiating susceptible strains from intermediate strains and the latter from resistant strains are as follows: S ≤1 mg/I and R > 4 mg/I.

The prevalence of acquired resistance in certain species can vary geographically and over time. It is therefore useful to have local information on resistance, especially in treating severe infections. These data are only guidelines indicating the probability of susceptibility of a bacterial strain to this antibiotic. When the prevalence of resistance of a bacterial species is known in France, it is indicated in the table below:

Category	Incidence of acquired resistance in France (> 10%) (range)
SUSCEPTIBLE SPECIES	
Gram-positive aerobic	
Bacillus cereus	
Corynebacterium diptheriae	
Enterococci	50 - 70 %
Rhodococcus equi	
Staphylococcus meti-S	
Staphylococcus meti-R*	70 - 80 %
Streptococcus B	
Unclassified streptococcus	30 - 40 %
Streptococcus pneumoniae	35 - 70 %
Streptococcus pyogenes	16 - 31 %
Gram-negative aerobic	
Bordetella pertussis	
Branhamella catarrhalis	
Campylobacter	
Legionella	
Moraxella	
Anaerobic	
Actinomyces	
Bacteroides	30 - 60 %
Eubacterium	
Mobiluncus	
Peptostreptococcus	30 - 40 %
Porphyromonas	
Prevotella	
Propionibacterium acnes	

Category	Incidence of acquired resistance in France (> 10%) (range)
Miscellaneous	
Borrelia burgdorferi	
Chlamydia	
Coxiella	
Leptospires	
Mycoplasma pneumoniae	
Treponema pallidum	
MODERATELY SUSCEPTIBLE SPECIES (intermediate susceptibility in vitro)	
Gram-negative aerobic	
Haemophilus	
Neisseria gonorrhoeae	

Anaerobic Clostridium perfringens **Miscellaneous** Ureaplasma urealyticum	
RESISTANT SPECIES **Gram-positive aerobic** Corynebacterium jeikeium Nocardia asteroïdes **Gram-negative aerobic** Acinetobacter Enterobacteries Pseudomonas **Anaerobic** Fusobacterium **Miscellaneous** Mycoplasma hominis	

Roxithromycin has in vitro and in vivo activity on Toxoplasma gondii.
In vitro, roxithromycin shows moderate activity on Mycobacterium avium.
* The incidence of methicillin resistance is approximately 30 to 50% for all staphylococci, and is mainly found in the hospital setting.

Microbiology
Roxithromycin is bacteriostatic at low concentrations and bactericidal at high concentrations. It binds to the 50S subunit of the 70S ribosome thereby disrupting bacterial protein synthesis.
A prolonged post antibiotic effect has been observed with roxithromycin. Whilst the clinical significance of this remains uncertain, it supports the rationale for once daily dosing. Although clinical data has demonstrated the efficacy and safety of once daily dosing in adults, this has not been demonstrated in children.
At plasma concentrations achieved with the recommended therapeutic doses, roxithromycin has been demonstrated to have *in vitro* and clinical activity against the following microorganisms:
Streptococcus pneumoniae, *Streptococcus pyogenes*, *Mycoplasma pneumoniae*, *Moraxella catarrhalis*, *Ureaplasma urealyticum*, Chlamydia spp.
Roxithromycin has been demonstrated to have clinical activity against the following microorganisms which are partially sensitive *in vitro* to roxithromycin:
Haemophilus influenzae, *Staphylococcus aureus* (except MRSA).

The following strains of microorganisms are resistant:
Multiresistant *Staphylococcus aureus*, Enterobacteriaceae, Pseudomonas spp., Acinetobacter spp.

Susceptibility Tests

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognized and standardized method (e.g. NCCLS). Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Using the NCCLS method of susceptibility testing with a 15mcg roxithromycin disc, susceptible organisms other than *Haemophilus influenzae* produce zones of inhibition 21mm or greater. A zone size of 10 to 20mm should be considered intermediate and a zone size of 9mm or less indicates resistance. A bacterial isolate may be considered susceptible if the MIC value for roxithromycin is less than or equal to 1 mg/L. Organisms are considered resistant if the MIC value is greater than 8 mg/L.

For *Haemophilus influenzae*, zones of inhibition 10 mm or greater indicate susceptibility when CO2 incubation and the HTM agar is used with a 15mcg roxithromycin disc. An isolate may be considered susceptible if the MIC value for roxithromycin is less than or equal to 8mg/L.

5.2 Pharmacokinetics

Absorption

Roxithromycin is absorbed after oral administration with an absolute bioavailability of approximately 50%. Peak plasma concentrations following administration of 150mg and 300mg film-coated tablets are achieved in young and elderly adult patients approximately 1 to 2 hours post-dose. However, Rulide D 50 mg tablets for suspension appear to be absorbed more slowly than the Rulide film-coated tablets, with peak plasma concentrations achieved approximately 3 hours post dose.

As food intake decreases absorption, Rulide should be administered at least 15 minutes before food or, alternatively, on an empty stomach (*i.e.* more than 3 hours after a meal). Absorption is not linear; with increasing doses in the range 150mg to 300mg, peak plasma levels and AUC do not increase in proportion to the dose.

After repeated administration of 2.5mg/kg every 12 hours to children, the average peak plasma concentration at steady state was 9mg/L and the AUC was 61mg.h/L.

Following administration of a single oral dose of Rulide 150 mg to healthy young adults, the mean peak plasma concentration was 6.6 mg/L and the AUC was 69mg.h/L. At steady state following doses of 150 mg twice daily, the mean peak plasma concentration was 9.3 mg/L and the AUC was 71mg.h/L.

In elderly patients, the mean peak plasma concentration following a single 150 mg dose was 9.1 mg/L and the AUC was 148mg.h/L. At steady state, a dosage regimen of 150 mg twice daily produced a mean peak plasma concentration of 11.3mg/L and an AUC of 83mg.h/L.

Following administration of a single oral dose of Rulide 300 mg to healthy young adults, the mean peak plasma concentration was 9.7 mg/L and the AUC was 98mg.h/L. At steady state following doses of 300 mg once daily, the mean peak plasma concentration was 10.9mg/L and the AUC was 77mg.h/L. In elderly patients, the mean peak plasma concentration following a single 300 mg dose was 10.8 mg/L and the AUC was 197mg.h/L.

Distribution

Roxithromycin is 92-96% bound to plasma proteins (principally alpha-1-acid glycoprotein, but also albumin) at concentrations less than 4.2mg/L. The binding is saturable: in subjects with normal plasma levels of alpha-1-acid glycoprotein, the extent of binding decreases when plasma concentrations of roxithromycin exceed 4.2mg/L. At a plasma concentration of 8.4mg/L, approximately 87% of the drug is protein bound.

Roxithromycin is highly concentrated in polymorphonuclear leucocytes and macrophages, where levels 30 times those in serum have been reported.

Metabolism

Roxithromycin undergoes limited metabolism in the body, presumably in the liver. The major metabolite is descladinose roxithromycin. Two minor metabolites have also been identified. Plasma levels of roxithromycin are approximately twice those of all metabolites; a similar ratio is approximately 7% of a dose is excreted in the urine and 13% is eliminated via the lungs. Faecal excretion, which represents the unabsorbed fraction and the small proportion excreted by the liver, accounts for approximately 53% of the dose. The fate of the remainder is unknown.

When roxithromycin plasma levels are above 4.2mg/L, renal clearance increases because reduced plasma protein binding causes increased levels of unbound roxithromycin, which may be excreted by the kidneys.

Elimination

The mean half-life of roxithromycin is approximately 12 hours in young adults and 20 hours in children. The apparently longer half-life in children does not cause excessive accumulation: C_{min} and AUC values are comparable for adults and children.

The half-life is prolonged to 25 hours in adults with impaired hepatic function and 18 hours in adults with renal insufficiency. The mean half-life in elderly patients is approximately 27 hours.

6 Pharmaceutical particulars

6.1 List of excipients

- Lactose
- Starch
- Starch for paste
- Gelatin
- Primojel
- Magnesium stearate
- Aerosil
- Opadry White
- PEG 6000
- Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C, and protect from moisture and direct sunlight.

6.5 Nature and contents of container

PVC /Aluminum foil blister strips.

Pack size: 1 × 10’s

6.6 Dispensing Requirements:

Roxysaf 150mg Tablet is dispensed only on the prescription of registered medical practitioner only.

7 Marketing authorization holder

Saffron Pharmaceuticals (Pvt.) Ltd.
19-Km, Sheikhupura Road, Faisalabad, Pakistan.